REMARKS

Claims 1-2 and 4-46 are pending in this application. Claims 5-7, 9-28, and 46 are withdrawn from consideration. After consideration of the remarks provided herein, claims 1-2 and 4-46 will remain pending in the application.

Claims 1, 2, 4, 8, and 29-45 are rejected under 35 U.S.C. § 103(a) over Billoni, et al., *Aeta Derm. Venereol.* 80:329-334 (2000) (hereinafter "Billoni") in view of Monneret et al., *J. Immunol.* 168:3563-3569 (2002) (hereinafter "Monneret"). The Office asserts that Monneret teaches that PGD_2 is a precursor to 15-deoxy-$\Delta^{12,14}$-PGJ_2 (hereinafter "15d-J_2") and that 15-deoxy-$\Delta^{12,14}$-PGD_2 ("15d-PGD_2") is an analog of PGD_2.[1] The Office further states that Billoni teaches that a high concentration of a PPAR-α ligand (such as clofribate) [2] leads to cessation of hair follicle growth *in vitro*, suggests that ligands specific for PPAR-α and PPAR-γ would yield similar results, and teaches that 15-deoxy-$\Delta^{12,14}$-PGJ_2 (hereinafter "15d-J_2") is a PPAR-γ specific ligand. Hence, the Office alleges that the "skilled artisan would have expected that 15d-PGD_2, the analog of its precursor would stimulate 15d-J_2 and trigger the alteration of human hair" (Final Rejection, page 3).

In rejecting Applicants' arguments in their April 7, 2008 response, the Office alleges that a mere hypothesis is a sufficient motivation or suggestion to make use of a PPAR-γ ligand to regulate hair growth and that the "claimed subject matter is the use of this suggestion" (Office Action, pages 3-4). Further, the Office asserts that there is a reasonable expectation of success based on Billoni's suggestion, but provides no other reasoning (Office Action, page 4).

Applicants respectfully assert that the claimed methods are non-obvious over Billoni and Monneret. As will be appreciated, a *prima facie case* of obviousness can be established by showing the following three criteria: 1) a suggestion or motivation to modify or combine the reference teachings; 2) a reasonable expectation of success; and 3) the teaching of all the claim limitations by the reference(s). M.P.E.P. § 2143. However, under some circumstances, the

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[1] Office Action of November 30, 2007.

[2] The Office actually states that a high concentration of PPAR-α leads to cessation of hair follicle growth *in vitro*,. Applicants assume that the Office meant a high concentration of a PPAR-α ligand, rather than a high concentration of the receptor.

inventive subject matter may be merely "obvious to try" but not obvious. *Medichem S.A. v. Rolabo S.L.*, 77 U.S.P.Q.2d 1865, 1871 (Fed. Cir. 2006). As the court explained:

> This admonition has been directed mainly at two kinds of error, namely where what would have been "obvious to try" would have been to vary all parameters or try each of numerous choices where the prior art gave no direction as to which of many possible choices is likely to be successful or to explore a promising field of experimentation, where the prior art gave only general guidance.

While Supreme Court has stated "obvious to try" may be enough to show obviousness under some circumstances, the Federal Circuit has cautioned that this standard will be difficult to apply where the art is unpredictable:

> …the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions…" In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." **To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.**

Eisai Co. Ltd. v. Dr. Reddy's Laboratory, Ltd., 87 USPQ2d 1452, 1457 (Fed. Cir. 2008) (citations removed). Hence, particularly in the chemical arts, when the prior art lacks "definiteness or certainty about the result", the inventive subject matter at most is "obvious to try", but not obvious. For example, in *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988), the court held that a claim was not obvious because none of the references cited by the Office suggested that two synthetic processes could be combined successfully to produce a product with the desired properties. Indeed, at least one expert was skeptical regarding the combination before the inventors "proved him wrong". *Id.* As the court cautioned, "[e]vidence that supports, rather than negates, patentability must be fairly considered". *Id.*

Applicants further note that obviousness cannot be predicated upon what is unknown. *In re Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977). For example, optimization of a variable cannot be obvious where one of ordinary skill in the art would not recognize that the variable will achieve a recognized result. *In re Yates*, 211 U.S.P.Q. 1149 (C.C.P.A. 1981) (holding that controlling the degree of conversion to optimize conversion of an acid-aldehyde ratio of the claimed reaction

would not have been obvious, where the prior art contained no express teaching of the relationship between the degree of conversion and the ratio of acid to aldehyde).

Applicants respectfully assert that the methods of reducing mammalian hair growth using a prostaglandin DP-receptor agonist, such as the elected species, 15-PGD_2, are non-obvious over Billoni and Monneret. First, Billoni does not establish that agonism at the PPAR-α receptor is responsible for hair growth cessation. As cautioned by the court in *Dow Chemical*, evidence that supports, rather than negates, patentability must be fairly considered. 5 U.S.P.Q.2d at 1532. Clofibrate, a PPAR-α receptor agonist, was found to increase hair follicle growth at low concentrations and reduce hair follicle growth a high concentrations. However, Billoni fails to identify a cause for the hair growth cessation at high concentrations stating that:

> The cause of hair growth cessation observed with…clofibrate **remains obscure** but **probably** cannot be accounted for by a toxic effect…

(Billoni, page 333, emphasis added). Thus, far from identifying an exact cause of the hair growth cessation, Billoni does not completely rule out a toxic effect not associated with agonism at the PPAR-α receptor. Hence, Billoni does not establish that there is a link between agonism at the PPAR-α receptor (rather than a toxic effect or modulation of some other receptor) and hair growth cessation, much less a link between agonism at the PPAR-γ receptor and hair growth cessation. Instead, as in *Dow Chemical*, Billoni demonstrates a lack of "definiteness or certainty" with regard to agonism at the PPAR-α receptor and hair growth reduction.

Given the obscurity of the cause of the hair growth cessation observed at high concentrations of clofibrate, a **PPAR-α** receptor agonist, one of ordinary skill in the art would not have a reasonable expectation that a **PPAR-γ** receptor agonist would reduce hair growth. As discussed above, Billoni characterizes clofibrate is a PPAR-α receptor ligand, not a PPAR-γ receptor ligand. Thus, there is a dearth of evidence in Billoni regarding the effect of a PPAR-γ receptor agonist on hair growth.

At most, Billoni represents speculation that alteration of the PPAR-controlled pathways – rather than agonism at a specific PPAR receptor – might be partially responsible for alteration of the hair cycle. As stated by Billoni:

> We can **hypothesize** from our results that this alteration in hair growth cycle **might be at least partially due to altered PPAR-controlled pathways**. This

> could be confirmed by using ligands other than clofibrate which are specific for the 2 other PPARs (-α and -γ) expressed in the human hair follicle.

(Billoni, page 333, emphasis added). Thus, for Billoni provides no specific guidance to one of ordinary skill that use of a PPAR-γ receptor agonist will result in hair growth cessation, rather than hair growth acceleration or both cessation and acceleration as observed for clofibrate. Instead, Billoni provides only general guidance to one of skill in the art and is replete uncertainty and indefiniteness regarding the ability of a PPAR-γ receptor agonist to reduce hair growth.

Even assuming *arguendo* that Billoni did provide a reasonable expectation of success that use of a PPAR-γ receptor agonist would result in hair growth reduction, the Office's obviousness rejection of claim 1 is improperly predicated upon what is unknown. In particular, as in *Yates*, there is absolutely no indication in Billoni or Monneret that an agonist of the prostaglandin DP-receptor would reduce hair growth. Billoni mentions 15d-PGJ_2 only in relation to its function as a ligand of PPAR-γ, but does not suggest that agonism at the prostaglandin DP-receptor would reduce hair growth. Hence, there is simply no reason for one of ordinary skill in the art to choose a PPAR-γ receptor agonist which is also a prostaglandin DP-receptor agonist, rather than a PPAR-γ receptor agonist which is not a prostaglandin DP-receptor agonist. Stated another way, the prior art provides no reason for narrowing the prior art universe of PPAR-γ receptor agonists to a finite number of dual PPAR-γ / prostaglandin DP-receptor agonists, particularly in light of the indefiniteness and uncertainty surrounding the role of PPAR-γ receptor agonism and hair growth reduction.

For all of these reasons, Applicants respectfully assert that the claims are non-obvious over Billoni and Monneret and request that the claim rejections be withdrawn.

Applicants respectfully submit that the claims are in condition for allowance and such action is respectfully requested.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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